CliffsNotes for Your DNA

Changing the chromatin binding domain of lens epithelium-derived growth factor changes how HIV reads the host genome and where it inserts its DNA.

"Let's imagine that the human genome is the text of a very important book on how to build a human being," said Stephen H. Hughes, Ph.D., Chief of the HIV Drug Resistance Program Retroviral Replication Laboratory at CCR. There are many different cell types in the human body, and each of the different cell types contains the same DNA sequences, the same set of instructions. The generation and proper maintenance of the different cell types requires that each cell knows which parts of the "book" to read.

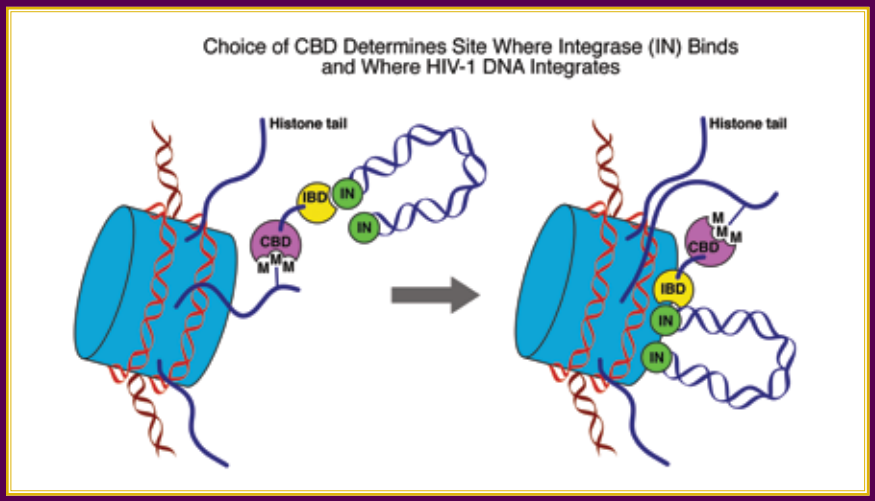
In humans, and all other eukaryotic organisms, genomic DNA is organized into chromatin. Annotations on the chromatin help define which parts of the genome a cell needs to read, and one of the important types of annotation are chemical modifications of the tails of histone proteins in the chromatin. In collaboration with researchers at the Rockefeller University and the Dana-Farber Cancer Institute, Hughes and his colleagues have found a way to redirect the integration of HIV-1 DNA via annotations and modifications to the chromatin.

"When we began working on this project, we knew, from the work of others, that HIV DNA did not integrate randomly, but preferred to integrate into the bodies of expressed genes," said Dr. Hughes. "We wanted to gain control over where HIV DNA integrates to make retroviral integration safer as a tool for gene therapy, and to develop a new method to investigate the chromatin organization and annotation."

HIV DNA integrates into actively expressed genes because the integration machinery binds to a host protein called lens epithelium-derived growth factor (LEDGF). LEDGF is a two-part protein made up of the chromatin binding domain (CBD), which binds to the host cell's chromatin, and the integrase binding domain (IBD), which binds the viral integration machinery. Thus, LEDGF acts as a tether linking the viral integration machinery to the host cell chromatin; the distribution of HIV integration sites reflects the distribution of LEDGF on host cell chromatin.

In the February 1, 2010 issue of *Proceedings of the National Academy of Sciences*, Dr. Hughes and colleagues reported that the integration site preference of HIV-1 can be changed by creating LEDGF fusion proteins in which the CBD is replaced by other CBDs that bind to different sites on host cell chromatin. These fusion proteins direct HIV integration to sites where the new CBDs bind.

"What it shows is we're not required simply to accept the distribution of HIV integration that nature provided; we can rewrite the rules," explained Dr. Hughes. This is important because HIV is a candidate virus for human gene therapy, and the researchers want to make sure that the viral DNA is inserted in safe places in the genome. Integration near an oncogene can activate the oncogene, causing cancer. Conversely, distribution of the binding sites for novel CBDs can be determined using HIV integration as a tool to mark the sites in the host genomes. This provides a powerful new tool for probing chromatin structure and function.



(Image: I. Kelly)

HIV-1 DNA (blue strands) integration into host DNA (red strands) depends on the composition of the chromatin binding domain (CBD).

To learn more about Dr. Hughes's *research, please visit his CCR Web site at* **http://ccr.cancer.gov/staff/staff.asp?Name=hughes**.